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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/656,140	09/08/2003	Yuanxiang Tao	001107.00388	8826

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

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09/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/656,140	TAO ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7,10-13,16-22,24,25,34,62 and 64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-7, 10-13, 16-22, 24, 25, 24, 34, 62, and 64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission mailed on August 30, 2007 has been entered.

Claims 1, 7, and 13 have been amended.

Claims 1, 4-7, 10-13, 16-22, 24, 25, 24, 34, 62, and 64 are pending in the instant application.

Claims 1, 4-7, 10-13, 16-22, 24, 25, 24, 34, 62, and 64 have been examined on the merits.

Response to Arguments

Applicant's Amendment and Response mailed August 30, 2007 have been considered. Rejections and/or objections not reiterated from the previous Office Action mailed April 2, 2007 are hereby withdrawn. Any arguments addressing said rejections and/or objections are moot. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Specification

It is noted that the instant specification at pages 26-32 lists numerous non-patent literature. If Applicants wish to have these references considered by the Office, Applicants should include them in an information disclosure statement filed under 37 CFR § 1.97.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-7, 10-13, 16-22, 24, 25, 24, 34, 62, and 64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4-7, 10-13, 16-22, 24, 25, 24, 34, 62, and 64 are indefinite because the term "PSD95" is not clearly defined. Since abbreviations often have more than one meaning, it is suggested that inserting the full name of the protein would overcome the instant rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-7, 10-13, 16-22, 24, 25, 24, 34, 62, and 64 are rejected under 35

U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claimed invention is drawn to a pharmaceutical composition comprising an antisense oligonucleotide which is complementary to mRNA encoding human PSD95 and methods for relieving or treating a condition in a human comprising administering an antisense oligonucleotide which is complementary to mRNA encoding human PSD95, wherein PSD95 expression is inhibited.

The instant specification teaches a single pharmaceutical antisense oligonucleotide corresponding to the PSD-95/DLG/Z0-1 (PDZ) domain, nucleotides 241 to 258 of rat PSD95/SAP90 mRNA represented as SEQ ID NO:1 in the instant invention. The prior art teaches an antisense oligonucleotide targeted to the PSD-95/DLG/Z0-1 (PDZ) domain, nucleotides 241 to 258 of rat PSD95/SAP90 (see Tao et al., NeuroReport, 2001 Vol. 12:3251-3255; Tao et al., Neuroscience, 2000 Vol. 98 :301-206 ; and Tao et al., Anesthesiology, 2001 Vol. 94:1010-1015). At the outset, it is noted that the rejected claims do not recite any sequence identifier relating to human PSD95. This sequence is thus considered to be defined by its function (i.e. the activity of human PSD95) rather than by any one specific structure. Accordingly, the claims embrace antisense oligonucleotides which are complementary to mRNA encoding human PSD95, or any such molecule with analogous human PSD95 activity, known or yet to be

discovered, along with any isoform or allele present within this species, or any variant, polymorphic or otherwise, that is within reasonable similarity from these families of proteins that retain human PSD95 activity.

To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Thus, an applicant complies with the written-description requirement by describing the invention, with all its claimed limitations, and by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical, structure/function correlation, methods of making the claimed product, and any combination thereof. The representative sample requirement may be satisfied by supplying structural or functional information, or a combination of both, such that one of skill in the art would be satisfied that applicants were in possession of the genus as claimed. Further, the size of the representative sample required is an inverse function of the unpredictability of the art.

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in

sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention.

Further, See MPEP § 2163, which states "[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

In order to synthesize the pharmaceutical antisense oligonucleotides which are complementary to mRNA encoding human PSD95, and practice the methods as claimed, one of skill would first need the sequence of the human PSD95. The instant specification teaches a single pharmaceutical antisense oligonucleotide corresponding to nucleotides 241 to 258 of rat PSD95/SAP90 mRNA represented as SEQ ID NO:1. However, the claims embrace antisense oligonucleotides which are complementary to mRNA encoding human PSD95, or any such molecule with analogous human PSD95

activity, known or yet to be discovered, along with any isoform or allele present within this species, or any variant, polymorphic or otherwise, that is within reasonable similarity from these families of proteins that retain human PSD95 activity.

Thus, because one of skill in the art could not envision any pharmaceutical antisense oligonucleotides which are complementary to mRNA encoding human PSD95, wherein the antisense inhibits expression of PSD95, other than SEQ ID NO:1 of the instant invention, one of skill would not be convinced that Applicants were in possession of the claimed invention at the time of filing, since functionality alone as recited in the instant claims does not elucidate the structure (e.g. nucleic acid sequence) of an antisense oligonucleotide having such function. It is noted that this functional limitation itself is not sufficient to provide a structure/function relationship for meeting the written description requirement because it is not clear what structure the antisense oligonucleotides which are complementary to mRNA encoding human PSD95 would have by the recitation of the functionality alone, "inhibits expression of PSD95". The specification provides no guidance in this regard. Apart from further experimentation, the skilled artisan would not have been able to predict the structures of the full scope of the pharmaceutical antisense oligonucleotides which are complementary to mRNA encoding human PSD95 encompassed by the instant invention, particularly in the absence of any teaching by way of structure or reference to active domains or regions. The genus is not immediately envisioned because the genus of antisense oligonucleotides which are complementary to mRNA encoding human PSD95 is considered to include not only the one sequence taught in the instant

invention, but also antisense oligonucleotides complementary to mRNA sequences with analogous human PSD95 activity, known or yet to be discovered. However, the distinguishing characteristics of the claimed genus are not considered to be described herein, or in the prior art.

Thus, because one of skill in the art could not envision any antisense oligonucleotide which is complementary to mRNA encoding human PSD95, other than the one sequence described in the instant specification, one of skill would not be convinced that Applicants were in possession of antisense oligonucleotides which are complementary to mRNA encoding human PSD95 sequences that are heretofore undescribed.

Response to Arguments

It is noted that a written description rejection was maintained in the Office Action mailed April 2, 2007. In response to the written description rejection mailed April 2, 2007, Applicants argue that the claims have been amended to recite an antisense oligonucleotide which is complementary to mRNA encoding human PSD95. Applicants contend that this amendment obviates the instant rejection.

This argument and contention have been fully considered, but are not found persuasive because, as discussed *supra*, the issue is that the rejected claims do not recite any sequence identifier relating to human PSD95. Therefore, the claims embrace antisense oligonucleotides which are complementary to mRNA encoding human PSD95, or any such molecule with analogous human PSD95 activity, known or yet to be

discovered, along with any isoform or allele present within this species, or any variant, polymorphic or otherwise, that is within reasonable similarity from these families of proteins that retain human PSD95 activity. The claims are directed to encompass a broad range of antisense oligonucleotides of highly variant structures (e.g. nucleic acid sequence), which have not been described in the specification and whose structure could not be envisioned by the skilled artisan based on the disclosure of the specification.

******

Claims 1, 4-7, 10-13, 16-22, 24, 25, 24, 34, 62, and 64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical formulation comprising an isolated and purified antisense polynucleotide which is complementary to PSD95 mRNA and comprises SEQ ID NO:1, and a method for relieving acute or chronic pain, treating or preventing hyperalgesia, or reducing a threshold for anesthesia comprising the intrathecally administration of an antisense oligonucleotide which is complementary to mRNA encoding human PSD95, wherein the antisense inhibits the expression of PSD95, and the antisense comprises SEQ ID NO:1, does not reasonably provide enablement for any pharmaceutical formulation comprising an isolated and purified antisense polynucleotide which is complementary to PSD95 mRNA or a method for relieving acute or chronic pain, treating or preventing hyperalgesia, or reducing a threshold for anesthesia comprising any route of administration of any antisense oligonucleotide which is complementary to mRNA

encoding human PSD95. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This is a scope enablement rejection.

There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claimed invention is drawn to a pharmaceutical formulation comprising an isolated and purified antisense polynucleotide which is complementary to PSD95 mRNA and a method for relieving acute or chronic pain, treating or preventing hyperalgesia, or reducing a threshold for anesthesia comprising administering an antisense oligonucleotide which is complementary to mRNA encoding human PSD95.

The nature of the claimed invention, therefore, requires the knowledge of using any route of administration of any antisense oligonucleotide which is complementary to mRNA encoding human PSD95 to inhibit human PSD95 expression in a human subject

to result in relieving chronic or acute pain or treating or preventing hyperalgesia.

The amount of direction or guidance and presence/absence of working examples:

The specification teaches the intrathecally administration of an antisense oligonucleotide corresponding to the PSD-95/DLG/Z0-1 (PDZ) domain, nucleotides 241 to 258 of rat PSD95/SAP90 (SEQ ID NO:1) inhibited PSD-95 expression (see Example 2), attenuated responses to pain, and lowered thresholds for anesthetics in Sprague-Dawley oligonucleotide-treated rats (see Figure 4 and Examples).

As per the 35 U.S.C. 112 first paragraph written description rejection above, the specification only teaches a single pharmaceutical antisense oligonucleotide that carries out the functionality of the instant claims.

The state of the prior art and the predictability or unpredictability of the art:

The prior art teaches that intrathecally administered antisense targeted to the PSD-95/DLG/Z0-1 (PDZ) domain, nucleotides 241 to 258 of rat PSD95/SAP90 inhibits PSD-95 expression, delays the development of neuropathic pain, and lowers thresholds for anesthetics in oligonucleotide-treated rats (see Tao et al., NeuroReport, 2001 Vol. 12:3251-3255; Tao et al., Neuroscience, 2000 Vol. 98 :301-206 ; and Tao et al., Anesthesiology, 2001 Vol. 94:1010-1015). In fact, Tao et al., NeuroReport, 2001 Vol. 12:3251-3255 teach, "the antisense ODN we designed can be safely used as a tool *in vivo*" (see page 3253, second column).

Although the specification and the prior art teach intrathecally administered antisense targeted to the PSD-95/DLG/Z0-1 (PDZ) domain, nucleotides 241 to 258 of rat PSD95/SAP90 inhibits PSD-95 expression, delays the development of neuropathic

pain, and lowers thresholds for anesthetics in Sprague-Dawley oligonucleotide-treated rats, neither the specification nor the prior art teach any other mode of delivery or any other effective antisense oligonucleotide.

The claims encompass any route of administration of the antisense oligonucleotide complementary to a mRNA encoding human PSD95, where the art has taught that delivering antisense *in vivo* is highly unpredictable. For example, the uptake of oligonucleotides by cells has been addressed by Agrawal, who states that "[o]ligonucleotides must be taken up by cells in order to be effective.... Cellular uptake of oligonucleotides is a complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (page 378).

Further, the claims are so broad to include systemic delivery where Nielsen, PE (Gene Therapy, 2005 Vol. 12:956-957) reviews the problems associated with nucleic acid-based therapeutics and systemic delivery. Nielsen, PE teach, "Many 'solutions' to this problem have been published on the subject during the last decade, but we yet have to see an effective delivery technology" (see page 956, second paragraph). Nielsen, PE also discuss that a major unmet challenge for the field is to develop methods that allow effective and simple cellular and especially systemic delivery of antisense agents. Nielsen, PE conclude by discussing the eager anticipation of both academic researchers and the pharmaceutical industry for delivery methods for gene therapy drugs.

Furthermore, the claims are so broad to encompass *in vivo* methods of using any antisense oligonucleotide which is complementary to mRNA encoding human PSD95 where is no guidance in the specification to suggest that other antisense oligonucleotides complementary to mRNA encoding human PSD95, other than SEQ ID NO:1, would be effective to result in relieving acute or chronic pain, treating or preventing hyperalgesia, or reducing a threshold for anesthesia as claimed. As discussed, for example, in Agrawal et al. and Tamm et al., it is unpredictable to determine the antisense ability of an oligonucleotide to inhibit target gene expression based purely on complementarity to a target mRNA. For example, Agrawal et al. (Molecular Medicine Today, 2000 Vol. 6:72-81), teach, "The initial step in selecting an antisense oligonucleotide is to choose an appropriate target sequence on the mRNA molecule. Antisense technology has been hampered to some extent by limited knowledge as to the base-pairing accessibility of mRNA target sites *in vivo*. Although a number of models that predict RNA folding are available, their use-fullness for predicting the most plausible *in vivo* RNA structure is limited" (see page 76, last paragraph). Agrawal et al. go on to teach, "The affinity of an oligonucleotide for its target RNA varies significantly depending on base composition and sequence. Therefore, the antisense activity of a selected oligonucleotide is influenced both by its base composition and by its sequence" (see page 77, second column, first paragraph). Therefore, the feasibility of antisense therapy for one antisense does not demonstrate the feasibility of antisense therapy for a wholly different antisense oligonucleotide, since the antisense activity of a selected oligonucleotide is influenced both by its base composition and by its sequence.

Tamm et al. (The Lancet., 2001, Vol. 358:489-497) teach that until "[T]he therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach.

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

The quantity of experimentation in this area of art is extremely large as it requires the analysis and *de novo* determination of how to systemically administer an antisense oligonucleotide to a human subject such that chronic pain is relieved or hyperalgesia is treated, for example. The quantity of experimentation in this area of art is extremely large as it also requires the analysis and *de novo* determination of those antisense oligonucleotides which are complementary to mRNA encoding human PSD95 that, upon administration, are effective in methods for relieving acute or chronic pain, treating or preventing hyperalgesia in a human subject. The prior art teaches that intrathecally administered antisense targeted to the PSD-95/DLG/Z0-1 (PDZ) domain, nucleotides 241 to 258 of rat PSD95/SAP90 inhibits PSD-95 expression, delays the development of neuropathic pain, and lowers thresholds for anesthetics in oligonucleotide-treated rats (see Tao et al., NeuroReport, 2001 Vol. 12:3251-3255; Tao et al., Neuroscience, 2000 Vol. 98 :301-206 ; and Tao et al., Anesthesiology, 2001 Vol. 94:1010-1015). The instant specification teaches an antisense oligonucleotide corresponding to the PSD-95/DLG/Z0-1 (PDZ) domain, nucleotides 241 to 258 of rat PSD95/SAP90 (SEQ ID

NO:1) inhibited PSD-95 expression, attenuated responses to pain, and lowered thresholds for anesthetics in Sprague-Dawley treated rats following intrathecal administration. As neither the prior art nor the specification provide guidance as to the structure of other antisense oligonucleotides which are complementary to mRNA encoding human PSD95 that function in the methods as claimed or how to systemically administer an antisense to a human subject to result in relieving acute or chronic pain or treating hyperalgesia, such analysis is replete with trial and error experimentation, with the outcome of each analysis being unpredictable. Screening each possible antisense oligonucleotide which is complementary to mRNA encoding human PSD95 to determine its ability to relieve acute or chronic pain or treat or prevent hyperalgesia is unpredictably undertaking in itself, with each of the many intervening steps, not providing any guarantee of success. Due to the scope of the claims, one of skill in the art would be required to further undertake extensive trial and error experimentation with a large number of subjects and controls, to determine how to deliver antisense oligonucleotides which are complementary to mRNA encoding human PSD95 to a human subject such that acute or chronic pain is relieved or hyperalgesia is treated or prevented.

Since the specification provides only guidance regarding a single pharmaceutical antisense oligonucleotide that functions in the methods as claimed, and since resolution of the various complications in regards to targeting a particular gene in an organism for gene therapy purposes is unpredictable, one of skill in the art would have been unable to practice the invention claimed without engaging in undue trial and error

experimentation.

Thus, given the broad claims in an art whose nature is identified as unpredictable, the state of the prior art, the lack of guidance in the specification, the breadth of the claims and the quantity of experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

It is noted that a scope of enablement rejection was maintained in the Office Action mailed April 2, 2007. In response to the enablement rejection mailed April 2, 2007, Applicants argue that nine references have been provided that review a sampling of the numerous clinical trails using a variety of antisense oligonucleotides that had been carried out and reported in the literature by the priority date of the instant application. Applicants contend that these references weigh heavily in favor of enablement and in this regard, the Office has not made a *prima facie* case that undue or unreasonable experimentation is needed to practice the claimed methods.

Applicant's arguments and contentions have been fully considered, but are not found persuasive. While the Examiner acknowledges the nine references that review a sampling of the numerous clinical trails using a variety of antisense oligonucleotides that had been carried out and reported in the literature by the priority date of the instant application, the particular antisense oligonucleotides taught in the nine references are not the same as that claimed in the instant invention. There may be, as Applicants

contend, some progress in the gene and antisense therapies, but the cited references, using totally different antisense than that claimed in the instant method, indicates that such successes are not the rule, but few and far between. As discussed above, the feasibility of gene or antisense therapy for one gene does not demonstrate the feasibility of gene or antisense therapy for a wholly different gene, as is the instant case.

Furthermore, Applicant is reminded that the claims are so broad to encompass systemic delivery of an antisense oligonucleotide which is complementary to mRNA encoding human PSD95 to a human subject. It is noted that of Applicant's nine references that review a sampling of the numerous clinical trails using a variety of antisense oligonucleotides that had been carried out and reported in the literature by the priority date of the instant application, eight of them reported intravenous delivery of various antisense oligonucleotides to human subjects. As discussed *supra*, due to the scope of the claims, one of skill in the art would be required to undertake extensive trial and error experimentation with a large number of subjects and controls, to determine how to systemically deliver antisense oligonucleotides which are complementary to mRNA encoding human PSD95 to a human subject such that acute or chronic pain is relieved or hyperalgesia is treated or prevented.

Thus, the *Wands* factors have been weighed and favor undue experimentation given the broad claims in an art whose nature is identified as unpredictable, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, and the teachings in the prior art balanced against the high skill level in the art. Therefore, it is the position of the Examiner that it

would require undue experimentation for one of skill in the art to perform the methods commensurate in scope with these claims.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

tcg
September 20, 2007

/Terra Cotta Gibbs/